Published in final edited form as:

J Natl Compr Canc Netw. 2014 December ; 12(12): 1706–1712.

Analysis of Recurrence Patterns in Acral versus Non-Acral Melanoma: Should Histologic Subtype Influence Treatment Guidelines?

Priyanka V. Gumaste, BA^{a,b}, Nathaniel H. Fleming, BA^{a,b}, Ines Silva, MD^{a,c}, Richard L. Shapiro, MD^{a,d}, Russell S. Berman, MD^{a,d}, Judy Zhong, PhD^a, Iman Osman, MD^{a,b,c}, and Jennifer A. Stein, MD, PhD^{a,b}

^aInterdisciplinary Melanoma Cooperative Group, New York University School of Medicine, New York, New York

^bRonald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York

^cDepartment of Medicine, New York University School of Medicine, New York, New York

^dDepartment of Surgery, New York University School of Medicine, New York, New York

Abstract

Background—Current surgical treatment of primary melanoma is uniform for all histo-subtypes, although certain types of melanoma, such as acral lentiginous melanoma (ALM), carry a poor prognosis. No study has explored the effectiveness of standard melanoma treatment guidelines in ALM compared to non-acral melanoma (NAM).

Methods—Study subjects were identified from a prospectively enrolled database of primary melanoma patients at **Blinded for Review Purposes**. ALM patients were matched to NAM patients (1:3) by gender and melanoma stage, including substage (ALM=61, NAM=183). All patients received standard of care treatment. Recurrence and survival outcomes in both cohorts were compared.

Results—ALM histologic subtype was an independent negative predictor of recurrence-free survival (HR = 2.45, $p < 0.001$) and melanoma-specific survival (HR= 2.64, $p = 0.001$) compared to NAM. Recurrence was significantly more common in ALM compared to NAM (49% versus 30%, $p=0.007$). In tumors less than 2mm in thickness, there was a significantly higher recurrence rate in ALM versus NAM ($p=0.048$). There was no significant difference in recurrence in tumors greater than 2mm ($p= 0.12$). Of note, the rate of loco-regional recurrence was nearly double in ALM compared to NAM ($p=0.001$).

Correspondence: Jennifer A. Stein, MD, PhD, New York University School of Medicine, 530 First Ave, Skirball 7R, New York, NY 10016. Jennifer.Stein@nyumc.org.

Conflicts of Interest: There are no relevant financial disclosures to report. Data presented in this paper has been submitted for presentation at the 2014 Association of Clinical Oncology National Meeting.

Data presented in this paper were submitted for presentation at the 2014 ASCO Annual Meeting, May 30–June 3, 2014.

Conclusions—Our data revealed a high rate of loco-regional failure in ALM compared to NAM when controlling for AJCC stage. Our results question whether ALM may require more aggressive surgical treatment than non-acral cutaneous melanomas of equal thickness, particularly in tumors less than 2mm thick. Revision of surgical margin recommendations based on larger multicenter cohorts may need to be considered.

INTRODUCTION

Acral lentiginous melanoma (ALM), which occurs on the palms, soles, or nail apparatus, accounts for approximately 2–10% of all melanomas¹. Although the incidence of ALM is similar across racial and ethnic groups, it represents a disproportionately high percentage of melanomas among darker-skinned patients.² Despite its relatively low incidence, ALM is particularly important because it carries a worse prognosis than other main melanoma subtypes.² The cause of this finding is controversial.^{2–15} In previous studies, poor outcomes in ALM have been explained by a delay in diagnosis^{8, 10, 16–18} due to its unusual and uncommon presentation. Several, more recent studies, however, have shown that ALM has worse survival outcomes than non-acral melanoma (NAM), even after controlling for melanoma stage.^{2, 19} This suggests that inherent molecular/biologic differences^{20–22} in ALM may also be contributing to poor outcomes.

One major limitation of these studies is a lack of data on recurrent disease due to inadequate patient follow-up. Given that recurrence is a critical predictive factor of patient survival, poor outcomes in ALM may be explained by differences in recurrence patterns between ALM and NAM. No studies have compared recurrence in ALM to NAM. However, two studies analyzing recurrence exclusively in ALM reported recurrence rates of 25–30%, with a majority of patients presenting with a local or regional recurrence in the involved extremity.^{5, 7} Possible risk factors for this finding include inadequate surgical margins, though margins less than 2 cm were not associated with an increased risk of loco-regional recurrence in one retrospective study.⁵

To date, no study has explored the effectiveness of standard melanoma treatment guidelines in ALM compared to NAM. In particular, though ALM carries a poor prognosis, it is not treated more aggressively than NAM; current surgical treatment guidelines are uniform for all melanoma histo-subtypes. In this study, we compare recurrence patterns and survival outcomes in ALM versus NAM in a stage-matched cohort of patients prospectively enrolled in the **Blinded for Review Purposes** Interdisciplinary Melanoma Cooperative Group (IMCG) database. We aim to integrate data on primary treatment, recurrence, and survival in order to raise the question of whether ALM tumors should require more aggressive surgical treatment than NAM tumors of equal thickness.

MATERIALS AND METHODS

Study Population

Patients who presented for treatment of primary invasive melanoma at **Blinded for Review Purposes** from September 2002 to August 2013 and provided written informed consent were prospectively enrolled in the Interdisciplinary Melanoma Cooperative Group (IMCG)

database. Study subjects were accrued within two months of primary melanoma treatment. All patients received wide local excisions with standard margins and a sentinel node biopsy if indicated by National Comprehensive Cancer Network (NCCN) guidelines. The Institutional Research Board at **Blinded** approved this study.

Clinical and demographic data including gender, race, age at first melanoma diagnosis, anatomic site of melanoma, and American Joint Committee on Cancer (AJCC) stage at diagnosis were recorded for each patient. The initial biopsy date of the primary tumor was used as the date of diagnosis; it was also used to calculate age at diagnosis, time to recurrence, and follow-up time. Surgical margin width, lymph node status, and histologic tumor characteristics including melanoma subtype, Breslow thickness, ulceration, and mitotic index were extracted from medical records. The IMCG pathologist, **Blinded for Review Purposes**, confirmed all tumor characteristics after review of slides to standardize all histological information in the database. Active prospective follow-up of all patients enrolled in the database was conducted every 6 months by IMCG staff. Recurrence and survival information was recorded for each patient.

Statistical methods

Each ALM patient (n=61) in the IMCG database was matched to three NAM patients (n=183) by gender and melanoma stage, including substage.¹⁹ ALM cases included melanomas arising from volar surfaces of the hands and feet as well as subungual melanoma. The NAM cohort was restricted to superficial spreading and nodular melanoma. Standard demographic variables (mean age at diagnosis and race) and prognostic indicators (Breslow thickness, sentinel lymph node status, ulceration, and mitosis) were compared between both groups to confirm an adequate match. A Fisher's exact/Chi-squared test was used for categorical variables and an independent sample T-test was used for continuous variables.

Melanoma-specific survival and recurrence-free survival were calculated for both cohorts using a Kaplan-Meier analysis. Survival was measured from the time of enrollment until a specified endpoint: death from melanoma in melanoma-specific survival, and any type of recurrence (local, regional, or distant) in recurrence-free survival. A multivariate Cox regression model stratified by melanoma type was used to calculate adjusted hazard ratios for melanoma-specific and recurrence-free survival. Hazard ratios were adjusted for unmatched risk factors such as Breslow thickness, mitotic index, ulceration, and sentinel lymph node status. A log-rank test was used to determine statistical significance.

Recurrence rates in ALM and NAM were compared using a Fisher's exact/Chi-squared test. Recurrence rates in both groups were also compared by tumor thickness. When stratifying our cohort, patient demographic and tumor characteristics were re-examined to ensure that there were no significant differences between both groups.

Location of first recurrence in each group was compared using a Fisher's exact test. The rate of local/regional recurrence versus distant recurrence was compared between ALM and NAM. A local/regional recurrence was defined to include local recurrences, satellite or in-transit metastases, and regional lymph node involvement. A distant recurrence was defined

as metastases to distant skin, lymph nodes, or viscera. In cases where patients experienced a local/regional recurrence and distant recurrence simultaneously, each recurrence was tabulated as a separate event.

IBM SPSS 21.0 was used for all statistical analyses. A *P*-value of less than 0.05 (two-tailed analysis) was used as the metric for statistical significance.

RESULTS

Clinical and pathological characteristics of our study cohort are illustrated in Table 1. Each ALM patient (n=61) was matched to three NAM patients (n=183) by gender and melanoma stage, including substage. A majority of patients were female (56%). Patients in our series ranged from stage I–III disease (I=34%, II=33%, III=33%). The mean Breslow thickness in the ALM and NAM groups was similar (ALM=2.52, NAM 2.51; *p*=0.278). There was no significant difference in mean age at diagnosis (ALM=61.7, NAM=62.9; *p*=0.252) and standard prognostic indicators (mitoses: *p*=0.60, ulceration: *p*=0.55, and sentinel lymph node positivity: *p*=0.68) between both cohorts. The only demographic that was not adequately matched was ethnicity. While a majority of patients in both cohorts were white, non-Hispanic (ALM=75%, NAM=96%), there were significantly more Black, Hispanic, and Asian patients in the ALM group (*p*<0.0001).

Patients in our series received standard of care treatment. All patients underwent surgical excision of their primary melanoma with a sentinel lymph node biopsy if indicated by standard guidelines.

ALM patients experienced poor survival outcomes compared to NAM patients

Kaplan-Meier analysis was used to determine melanoma-specific survival in our series. The median follow-up time for the ALM and NAM cohorts were 33 months and 58 months, respectively. There was a statistically significant decrease in melanoma-specific survival in ALM compared to NAM (Figure 1). The ALM cohort demonstrated a lower median melanoma-specific survival time (82.1 months) compared to the NAM group (>200 months, *p*=0.004). In the NAM group, the median melanoma-specific survival time has not yet been reached.

A multivariate Cox regression model was used to evaluate whether ALM histologic subtype was an independent predictor of melanoma-specific survival. After adjusting for unmatched prognostic indicators such as Breslow thickness, mitotic index, sentinel lymph node status, and ulceration, our results showed that ALM was an independent negative predictor of melanoma-specific survival (HR = 2.64, *p* = 0.001) compared to NAM.

Recurrence was significantly more common in ALM, particularly in tumors less than 2mm in thickness

Recurrence data for our cohort is shown in Table 2. Recurrence was significantly more common in ALM compared to NAM (49% versus 30%, *p*=0.007). Additionally, we compared recurrence rates by tumor thickness in both cohorts because surgical treatment of primary melanoma is based on tumor thickness: for tumors greater than 2mm in thickness, a

2cm surgical margin is recommended, while for tumors less than 2mm, a surgical margin between 1cm and 2cm is acceptable.²³ When stratifying our cohort by tumor thickness, we re-examined patient demographic and tumor characteristics between the ALM and NAM groups to ensure that both groups were not significantly different. In tumors less than 2mm in thickness, there was a significantly higher recurrence rate in ALM (28%) versus NAM (10%, $p=0.048$). In tumors greater than 2mm, the rate of recurrence was elevated in ALM compared to NAM, though non-significant (ALM=64%, NAM=47%, $p=0.12$).

Recurrence-free survival in both groups was calculated using a Kaplan-Meier analysis to determine median time to recurrence. The median recurrence-free survival time in ALM was 47.1 months, compared to 213.5 months in NAM ($p<0.001$, Figure 2). After performing a multivariate analysis, our data revealed that ALM histologic subtype was an independent negative predictor of recurrence-free survival compared to NAM (HR = 2.45, $p < 0.001$).

There were no significant differences in ALM and NAM patients who experienced a recurrence, in terms of demographic and primary lesion clinical parameters. The mean age of recurrence in ALM was 61.0 years compared to 66.3 years in NAM ($p=0.06$). The mean primary tumor thickness of recurred patients in both groups was also similar (ALM=3.28mm, NAM= 3.95mm; $p=0.201$). There was no significant difference in mitoses ($p=0.2$), ulceration ($p=0.82$), or lymph node status ($p=0.82$) between both groups. Additionally, when analyzing only the subset of recurred patients, there was no significant difference in melanoma-specific survival time between both groups (ALM vs. NAM adjusted HR = 1.14, $p = 0.67$).

The rate of loco-regional failure was nearly double in ALM compared to NAM

Location of first recurrence was examined by comparing local/regional recurrence to distant recurrence in both cohorts (Table 2). In cases where patients presented with a local/regional recurrence and distant recurrence simultaneously—for example, regional skin and distant lymph node involvement—each recurrence was tabulated as a separate event. Our data demonstrated that the rate of loco-regional recurrence was nearly double in ALM (39%) compared to NAM (19%, $p=0.001$, Figure 3). The rate of distant metastasis was similar in both groups (ALM: 16%, NAM: 15%, $p=0.84$).

DISCUSSION

In this study, we have demonstrated that ALM has higher recurrence rates and poor survival outcomes compared to NAM, after controlling for melanoma stage. Poor outcomes in ALM have been explained by several hypotheses, including a delay in diagnosis. This would lead to diagnosis at an advanced stage, with thicker primary tumors and delayed treatment.^{24, 25} We have shown that even after accounting for these factors, ALM patients experienced worse outcomes compared to their NAM counterparts. ALM patients in our series were 1.6-times more likely to experience a recurrence and developed a recurrence approximately 3-fold sooner than NAM patients. Additionally, they were approximately 2.5-times more likely to die from melanoma. Though several studies have shown that ALM has poor survival outcomes compared to NAM,^{2, 4, 19} recurrence patterns between both groups have

not been compared. To date, our study is the first to integrate data on primary treatment, recurrence, and survival in ALM versus NAM.

A high rate of loco-regional failure in ALM compared to NAM when controlling for AJCC stage is a unique finding in our study. Our results are concordant with previous studies analyzing recurrence exclusively in ALM that reported recurrence rates of 25–30%, with most patients presenting with a loco-regional failure.^{5, 7} Interestingly, in our series, the rate of distant metastases was similar in ALM and NAM, despite the fact that ALM patients experienced worse survival outcomes. To further elucidate the role of recurrence in survival in ALM, we compared melanoma-specific survival in patients who experienced a recurrence in both cohorts and demonstrated that survival was similar. Overall, these results suggest that recurrence rate, not location of first recurrence, contributes to worse survival outcomes in ALM. By this logic, decreasing loco-regional recurrence would decrease the overall recurrence rate in ALM, which may improve survival.

The high rate of loco-regional failure in our series leads us to question whether ALM may require wider surgical margins than non-acral cutaneous melanomas of equal thickness. Widening surgical margins in ALM may not be beneficial for thicker tumors, but may decrease recurrence in tumors less than 2mm in thickness, as these tumors had a significantly elevated recurrence rate compared to NAM in our series. Current National Comprehensive Cancer Network (NCCN) guidelines are uniform for all melanoma subtypes. A 1cm surgical margin is recommended for tumors 1mm or less in thickness. For tumors between 1mm-2mm, a surgical margin between 1cm and 2cm is acceptable. For lesions 2mm or greater, a 2cm margin is recommended.²³ Several prior studies have shown that widening surgical margins in melanomas between 1mm-4mm in thickness decreases the rate of loco-regional failure, but does not impact survival.^{26, 27} Other clinical trials have shown that widening surgical margins does not improve local control of primary invasive melanoma.^{28–33} All of these studies, however, exclude ALM. Though one retrospective study investigated the association between loco-regional recurrence and surgical margins less than 2cm in ALM, no association was reported likely due to inadequate sample size.¹⁷ Our results suggest that in ALM, improved loco-regional control by widening surgical margins may in fact correlate with improved survival outcomes.

ALM tumors have been shown to demonstrate unique genomic aberrations,^{20–22} suggesting that ALM invasion and progression may be biologically distinct from other cutaneous melanomas. NAM patients in our cohort experienced a higher proportion of distant metastasis, suggesting that improved local control with a more extensive surgical resection would not have a major impact on survival. Targeted systemic therapy might be more beneficial in these patients. In ALM, where a majority of recurrences were loco-regional, patients might benefit from a more extensive surgical resection. Arguments against widening surgical margins include increased morbidity in a sensitive site where achieving even appropriate margins may be difficult. However, wider surgical margins may prevent subsequent re-excisions due to recurrences, thereby decreasing long-term morbidity.

In summary, our data revealed a high rate of loco-regional failure in ALM compared to NAM when controlling for all standard prognostic indicators. Our results suggest that ALM

is a uniquely aggressive melanoma subtype that may require specially-tailored treatment. Our results question if current surgical treatment guidelines are adequate in ALM, though we cannot make any recommendations without further investigation. Revision of surgical margin recommendations based on larger multicenter cohorts may need to be considered. Though independent validation in a different subset of patients is needed to confirm our findings, our results highlight pronounced differences in recurrence and survival between ALM and NAM and identify key areas for future research.

CONCLUSION

Overall, our data demonstrates that a high rate of loco-regional failure in ALM may contribute to a decrease in melanoma-specific survival in these patients. ALM is an aggressive melanoma variant that may require uniquely tailored therapy. Our results call into question the current surgical guidelines for management of ALM.

Acknowledgments

Ms. Gumaste, Mr. Fleming, and Drs. Silva, Shapiro, Berman, Zhong, Osman, and Stein participated in the drafting of the manuscript and critical revision of the manuscript for important intellectual content. NCI Cancer Center Support Grant (5 P30 CA 016087- 27) to the Perlmutter Cancer Center at New York University and the Marc Jacobs Campaign to support melanoma research were funding sources for this paper. Dr. Stein was supported by the Irwin I. Lubowe Fellowship in Dermatology.

References

1. Agarwala, SS.; Kirkwood, JM. Melanoma: Epidemiology. In: Joseph, RB., editor. Encyclopedia of Cancer. 2. New York: Academic Press; 2002. p. 153-166.
2. Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986–2005. Arch Dermatol. 2009; 145:427–434. [PubMed: 19380664]
3. Kuchelmeister C, Schaumburg-Lever G, Garbe C. Acral cutaneous melanoma in caucasians: clinical features, histopathology and prognosis in 112 patients. Br J Dermatol. 2000; 143:275–280. [PubMed: 10951133]
4. Slingluff CL Jr, Vollmer R, Seigler HF. Acral melanoma: a review of 185 patients with identification of prognostic variables. J Surg Oncol. 1990; 45:91–98. [PubMed: 2214797]
5. Egger ME, McMasters KM, Callender GG, et al. Unique prognostic factors in acral lentiginous melanoma. Am J Surg. 2012; 204:874–879. discussion 879–880. [PubMed: 23022254]
6. Phan A, Touzet S, Dalle S, Ronger-Savle S, Balme B, Thomas L. Acral lentiginous melanoma: histopathological prognostic features of 121 cases. Br J Dermatol. 2007; 157:311–318. [PubMed: 17596173]
7. Phan A, Touzet S, Dalle S, Ronger-Savle S, Balme B, Thomas L. Acral lentiginous melanoma: a clinicoprognostic study of 126 cases. Br J Dermatol. 2006; 155:561–569. [PubMed: 16911282]
8. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998; 83:1664–1678. [PubMed: 9781962]
9. Paladugu RR, Winberg CD, Yonemoto RH. Acral lentiginous melanoma. A clinicopathologic study of 36 patients. Cancer. 1983; 52:161–168. [PubMed: 6850538]
10. Ridgeway CA, Hieken TJ, Ronan SG, Kim DK, Das Gupta TK. Acral lentiginous melanoma. Arch Surg. 1995; 130:88–92. [PubMed: 7802583]
11. Sondergaard K. Histological type and biological behavior of primary cutaneous malignant melanoma. 2. An analysis of 86 cases located on so-called acral regions as plantar, palmar, and

- sub-/parungual areas. *Virchows Arch A Pathol Anat Histopathol.* 1983; 401:333–343. [PubMed: 6415910]
12. Gutman M, Klausner JM, Inbar M, Skornick Y, Baratz M, Rozin RR. Acral (volar-subungual) melanoma. *Br J Surg.* 1985; 72:610–613. [PubMed: 4027531]
  13. Scrivner D, Oxenhandler RW, Lopez M, Perez-Mesa C. Plantar lentiginous melanoma. A clinicopathologic study. *Cancer.* 1987; 60:2502–2509. [PubMed: 3664431]
  14. Shaw JH, Koea JB. Acral (volar-subungual) melanoma in Auckland, New Zealand. *Br J Surg.* 1988; 75:69–72. [PubMed: 3337957]
  15. Vazquez M, Ramos FA, Sanchez JL. Melanomas of volar and subungual skin in Puerto Ricans. A clinicopathologic study. *J Am Acad Dermatol.* 1984; 10:39–45. [PubMed: 6693598]
  16. Cascinelli N, Zurrida S, Galimberti V, et al. Acral lentiginous melanoma. A histological type without prognostic significance. *J Dermatol Surg Oncol.* 1994; 20:817–822. [PubMed: 7798414]
  17. Jimbow K, Takahashi H, Miura S, Ikeda S, Kukita A. Biological behavior and natural course of acral malignant melanoma. Clinical and histologic features and prognosis of palmoplantar, subungual, and other acral malignant melanomas. *Am J Dermatopathol.* 1984; 6 (Suppl):43–53. [PubMed: 6528942]
  18. Weyers W, Euler M, Diaz-Cascajo C, Schill WB, Bonczkowitz M. Classification of cutaneous malignant melanoma: a reassessment of histopathologic criteria for the distinction of different types. *Cancer.* 1999; 86:288–299. [PubMed: 10421265]
  19. Bello DM, Chou JF, Panageas KS, et al. Prognosis of Acral Melanoma: A Series of 281 Patients. *Ann Surg Oncol.* 2013
  20. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005; 353:2135–2147. [PubMed: 16291983]
  21. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol.* 2006; 24:4340–4346. [PubMed: 16908931]
  22. Miracco C, Santopietro R, Biagioli M, et al. Different patterns of cell proliferation and death and oncogene expression in cutaneous malignant melanoma. *J Cutan Pathol.* 1998; 25:244–251. [PubMed: 9696289]
  23. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet.* 2005; 365:687–701. [PubMed: 15721476]
  24. O'Leary JA, Berend KR, Johnson JL, Levin LS, Seigler HF. Subungual melanoma. A review of 93 cases with identification of prognostic variables. *Clin Orthop Relat Res.* 2000;206–212. [PubMed: 10986996]
  25. Tan KB, Moncrieff M, Thompson JF, et al. Subungual melanoma: a study of 124 cases highlighting features of early lesions, potential pitfalls in diagnosis, and guidelines for histologic reporting. *Am J Surg Pathol.* 2007; 31:1902–1912. [PubMed: 18043047]
  26. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. *N Engl J Med.* 2004; 350:757–766. [PubMed: 14973217]
  27. Hudson LE, Maithel SK, Carlson GW, et al. 1 or 2 cm margins of excision for T2 melanomas: do they impact recurrence or survival? *Ann Surg Oncol.* 2013; 20:346–351. [PubMed: 23010731]
  28. Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. *Ann Surg Oncol.* 2001; 8:101–108. [PubMed: 11258773]
  29. Balch CM, Urist MM, Karakousis CP, et al. Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. *Ann Surg.* 1993; 218:262–267. discussion 267–269. [PubMed: 8373269]
  30. Cohn-Cedermark G, Rutqvist LE, Andersson R, et al. Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8–2.0 mm. *Cancer.* 2000; 89:1495–1501. [PubMed: 11013363]
  31. Karakousis CP, Balch CM, Urist MM, Ross MM, Smith TJ, Bartolucci AA. Local recurrence in malignant melanoma: long-term results of the multiinstitutional randomized surgical trial. *Ann Surg Oncol.* 1996; 3:446–452. [PubMed: 8876886]

32. Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. *Arch Surg.* 1991; 126:438–441. [PubMed: 2009058]
33. Veronesi U, Cascinelli N, Adamus J, et al. Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. *N Engl J Med.* 1988; 318:1159–1162. [PubMed: 3079582]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Kaplan-Meier curve of Melanoma-Specific Survival in ALM and NAM: Melanoma-specific survival time was decreased in ALM compared to NAM. The ALM cohort demonstrated a lower median melanoma-specific survival (82.1 months) compared to the NAM group (>200 months, $p=0.004$).

Figure 2.

Kaplan-Meier curve of Recurrence-Free Survival in ALM and NAM: Patients with ALM experienced a decreased recurrence- free survival compared to NAM. Median recurrence-free survival time was 47.1 months in ALM compared to 213.5 months in NAM ($p < 0.001$).

Figure 3.

Recurrence Rates in ALM and NAM: Recurrence was significantly more common in ALM compared to NAM (49% versus 30%, $p=0.007$). The rate of loco-regional recurrence was nearly double in ALM (39%) compared to NAM (19%, $p=0.001$).

Table 1

Patient Demographic and Histological/Clinical Tumor Characteristics of All Patients in Matched Cohort

	Acral melanoma (ALM) N=61	Non-Acral melanoma (NAM) N=183	p value
Gender			
Male	27 (44%)	81 (44%)	p=1
Female	34 (56%)	102 (56%)	
Age			
Mean (Range)	61.7 (32–90)	62.9 (27–91)	p=0.252
Median Follow-up	33 months	58 months	
Race/Ethnicity			
White, Nonhispanic	45 (74%)	176 (96%)	p<0.0001
Black or African American	7 (11%)	1 (0.5%)	
White, Hispanic	5 (8%)	5 (3%)	
Asian	4 (7%)	1 (0.5%)	
Stage			
IA	11 (18%)	33 (18%)	p=1
IB	10 (16%)	30 (16%)	
IIA	12 (20%)	36 (20%)	
IIB	5 (8%)	15 (8%)	
IIC	3 (5%)	9 (5%)	
IIIA	5 (8%)	15 (8%)	
IIIB	11 (18%)	33 (18%)	
IIIC	4 (7%)	12 (7%)	
Thickness (mm)			
0–1	13 (21%)	46 (25%)	p=0.278
1.01–4	37 (61%)	107 (58%)	
4.01+	11 (18%)	30 (16%)	
Mean	2.52	2.51	
Median	2.38	2.10	
Mitoses			
Present	40 (66%)	132 (72%)	p=0.60
Absent	18 (29%)	50 (27%)	
Unclassified	3 (5%)	1 (1%)	
Ulceration			
Present	26 (43%)	70 (38%)	p=0.55
Absent	35 (57%)	113 (62%)	
Positive Sentinel Lymph Node			

	Acral melanoma (ALM) N=61	Non-Acral melanoma (NAM) N=183	p value
Yes	19 (31%)	52 (28%)	p=0.68
No	42 (69%)	131 (72%)	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Recurrence and Survival Data of All Patients in Matched Cohort

	Acral melanoma (ALM) N=61	Non-Acral melanoma (NAM) N=183	p value
Recurrence			
Yes	30 (49%)	55 (30%)	p=0.007
No	31 (51%)	128 (70%)	
Recurrence rate by Tumor Thickness			
Less or equal to 2mm	7/25 (28%)	9/86 (10%)	p=0.048
Greater than 2mm	23/36 (64%)	46/97 (47%)	p= 0.12
First Recurrence Site			
Local/Regional	24/61 (39%)	34/183 (19%)	p=0.001
Distant	10/61 (16%)	28/183 (15%)	p= 0.84